AD_____

Award Number: DAMD17-02-1-0423

TITLE: Molecular Basis for the Toxicity of Schweinfurthins to Breast Cancer Cells

PRINCIPAL INVESTIGATOR: Jeffrey D. Neighbors
David Wiemer, Ph.D.

CONTRACTING ORGANIZATION: University of Iowa
Iowa City, Iowa 52242

REPORT DATE: May 2003

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	May 2003	Annual Summary (18 Apr 02 - 17 Apr 03)

4. TITLE AND SUBTITLE
Molecular Basis for the Toxicity of Schweinfurthins to Breast Cancer Cells

5. FUNDING NUMBERS
DAMD17-02-1-0423

6. AUTHOR(S)
Jeffrey D. Neighbors
David Wiemer, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Iowa
Iowa City, Iowa 52242

E-Mail: Jeffrey-neighbors@uiowa.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)

The schweinfurthins are a small set of diprenylated stilbenes isolated from an African plant. Schweinfurthins A, B, display significant and unique activity in the NCI's 60 cell line panel, and the breast cancer lines MCF7 and HS 578T were among the most sensitive. To study the mechanism of action and provide a reliable source, a chemical synthesis has been initiated. Two similar cationic cyclization routes have been explored one of which holds promise of giving enantiopure material. The very advanced compound 3-deoxyschweinfurthin B has been synthesized in enantioenriched form and is currently undergoing bioassay at the NCI. This compound demonstrates the viability of our over synthetic strategy and will give valuable information pertaining to the chemical nature of the activity in these compounds.

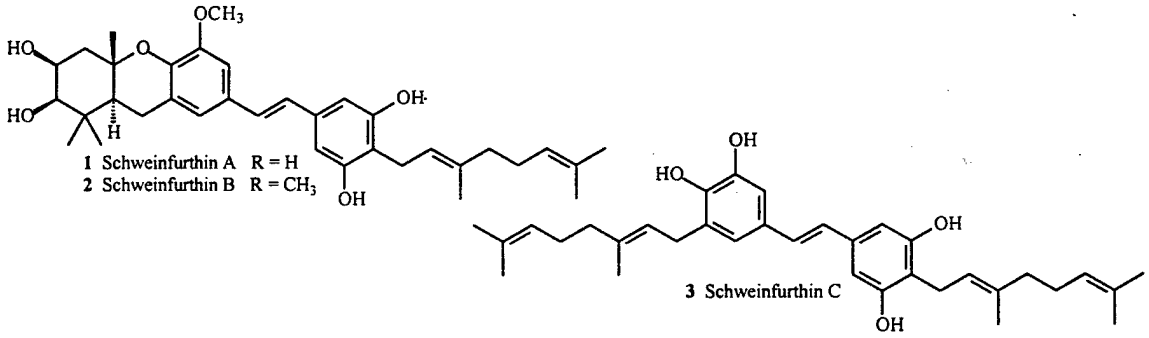
14. SUBJECT TERMS	15. NUMBER OF PAGES
Schweinfurthin, natural products, drug development	15
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

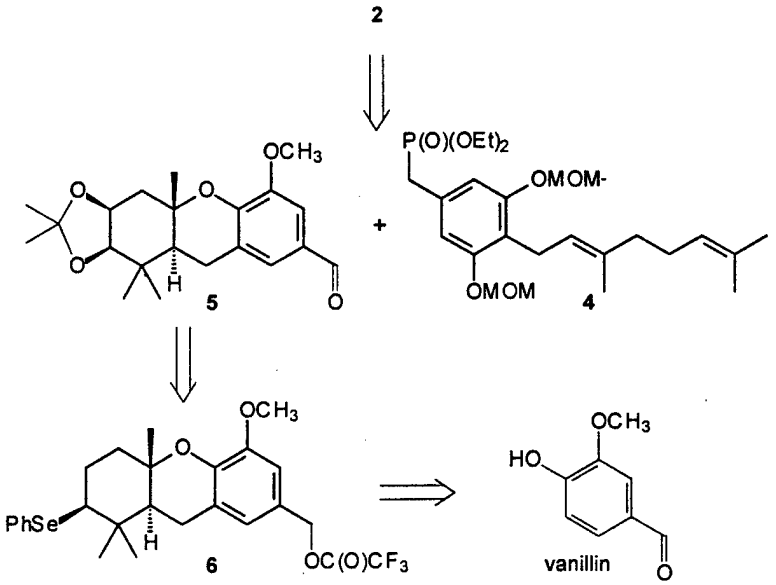
Introduction:

The schweinfurthins (**1–3**) are a small set of diprenylated stilbenes isolated from the African plant *Macaranga schweinfurthii* Pax. by Beutler *et al.* at the National Cancer Institute.[1,2] Schweinfurthins A (**1**), B (**2**), display significant activity in the NCI's 60-cell line anticancer assay with GI_{50}'s of less than 0.5 μM. Among the most sensitive cell lines were the breast cancer lines MCF7 and HS 578T. Inspection of the spectrum of activity shows no correlation with any currently used agents suggesting that these compounds may be acting at a previously unrecognized target or through a novel mechanism. The schweinfurthins have been isolated in low and varying amounts from the natural source, and their absolute stereochemistry has yet to be elucidated. For these reasons as well as their interesting biological activity, we have undertaken a total synthesis effort. An eventual asymmetric synthesis will allow assignment of the absolute stereochemistry and will provide a reliable source of schweinfurthins for further testing. Further chemical synthesis will eventually allow access to analogs designed to probe the biological activity of these compounds.



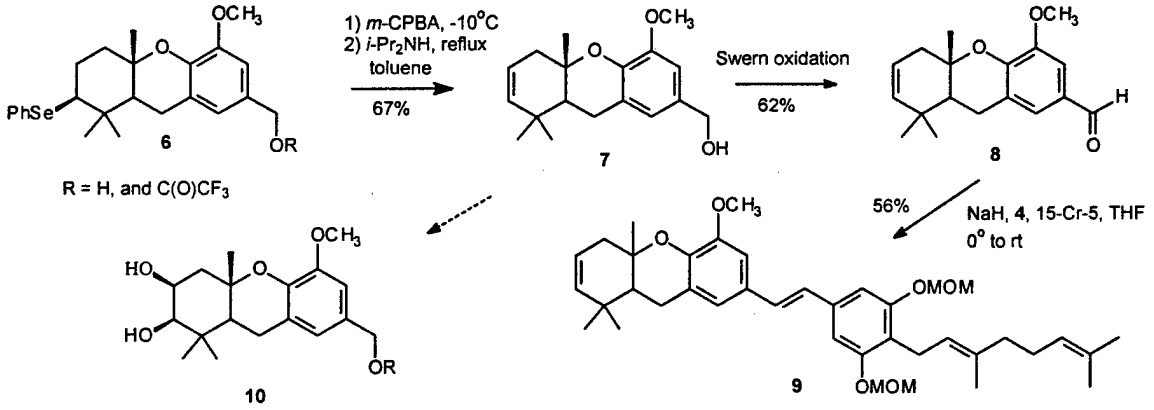
Body.

Our synthetic strategy (shown below) is based upon a convergent approach aimed at Schweinfurthin B where the central stilbene olefin is constructed at a late stage. This approach should allow for ease of introduction of differing functionality, and access to numerous analogs for potential mechanism of action probes.

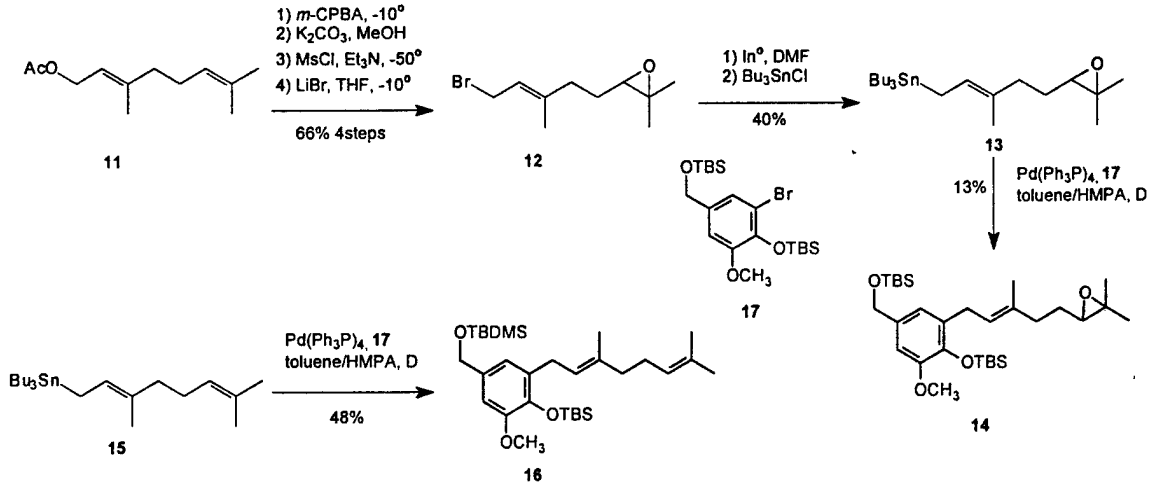


We have demonstrated the feasibility of such a strategy using a Horner-Wadsworth-Emmons condensation to introduce the stilbene bond in the inactive member of the class schweinfurthin C **3**.[3] The "right-half" phosphonate **4**, can be conserved for the synthesis of schweinfurthin B without modification. All of the active schweinfurthins require a hydroxylated "left-half" core represented in the protected aldehyde **5**. The synthesis of phenylselenide **6**, an advanced precursor to this aldehyde has been reported in a previous communication (Appendix).[4] This report will focus on subsequent modifications of **6**, as well as our work on introducing absolute stereocontrol into the synthetic scheme.

Compound **6** is now available via an 11-step sequence from vanillin in approx. 10% yield (see Appendix). Treatment of the selenide **6** under standard selenoxide elimination conditions has afforded the olefin **7.** We have explored several methods for introduction of the dihydroxyl system (i.e. compound **10**), but so far this goal has eluded our efforts. However, treatment of the benzyl alcohol **7** under Swern oxidation conditions gives aldehyde **8** which upon treatment under Horner-Wadsworth-Emmons conditions gives the protected stilbene **9**. This validates our overall coupling strategy and after removal of the MOM groups will give a compound that we will send for biological evaluation.

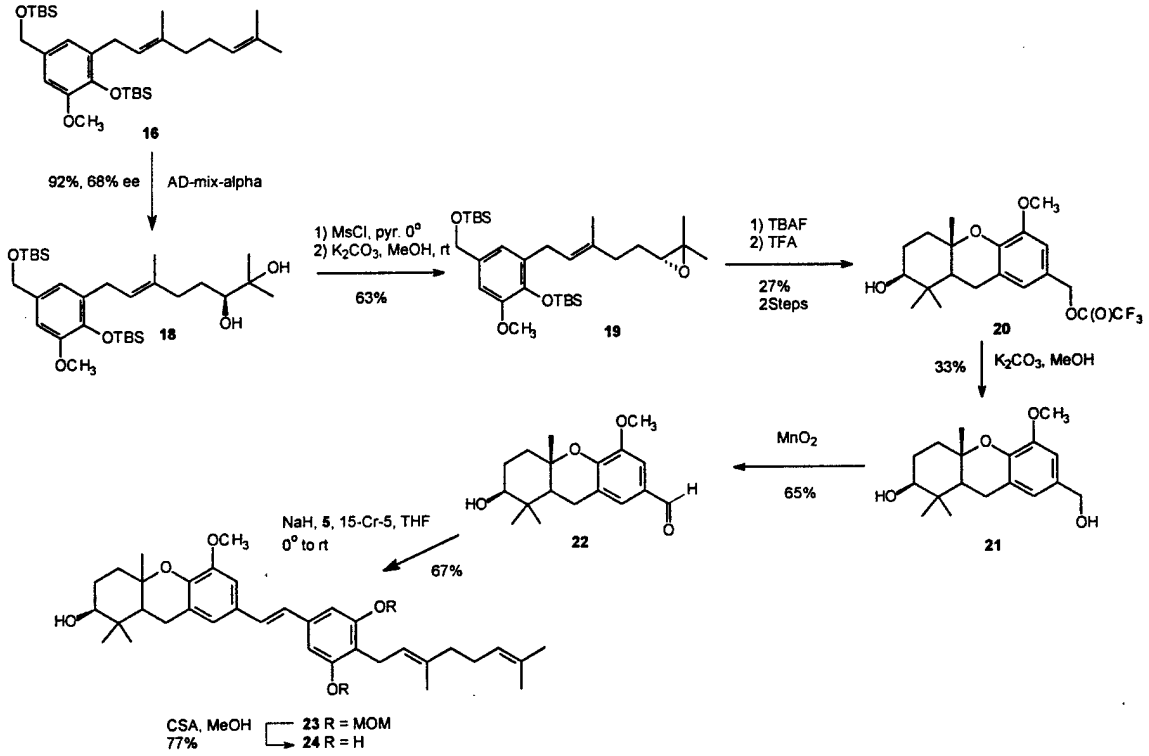


While some efforts have been expended in the area of the racemic synthesis and introduction of the hydroxyl groups into compound **7**, more promising results have been noted in our nonracemic synthetic endeavors. We initially explored synthesizing nonracemic geranyl derivatives with the hope of introducing them into the synthesis of our phenylselenide system. To this end the epoxygeranyl bromide **12**, which is known in enantiopure form[5], was produced as a racemate by epoxidation of geranyl acetate **11**, with subsequent deprotection and formation of the bromide via



the mesylate. The bromide **12** was treated with indium in dimethyl formamide; following treatment of the resulting solution with tri-butyltin chloride to induce transmetallation the epoxy stannane **13** was isolated in low yield.[6] After some exploration the treatment of aryl bromide **17** with this tin reagent under Stille conditions afforded a low yield of aryl epoxide **14**. Given the low yield of this coupling we attempted coupling with geranyl tri-butyl tin. Treatment of the silyl ether **17** with stannane **15** under similar conditions did afford a moderate yield of the desired geranylated arene **16**. This route as it stands represents an improvement over the previously disclosed alternative route to compound **16**.[4] Efforts to further optimize and expand the scale of this Stille coupling tactic are underway.

The low yield obtained in the coupling that gave epoxide **14** led us to search for alternative methods to introduce this functionality into silyl ether **16** in a stereoselective manner. There is literature precedent for selective dihydroxylation of the terminal olefin of a geranyl chain in simple systems such as geraniol itself, and it appeared as though steric and electronic factors would favor this outcome on our system.[7]



To our delight, as shown above, treatment of geranylated arene **16** with a Sharpless asymmetric dihydroxylation reagent affords an excellent yield of the diol **18.** The stereochemistry of this diol was proven via a Mosher-Trost analysis of the *O*-methyl mandelate ester of the secondary alcohol. Diol **18** can easily be transformed into the enantionenriched epoxide **19** which could be used to make enantioenriched phenylselenide and complete our previous tricycle synthesis. However we opted first to test the potential for the epoxide to undergo a cationic cyclization. Removal of the silyl ethers from compound **19** followed by treatment with trifluoroacetic acid did in fact give the tricycle **20**. Removal of the TFA ester and selective oxidation of the benzylic alcohol with manganese dioxide led to the aldehyde **22**. This aldehyde was subjected to our Horner-Wadworth-Emmons conditions to give the protected stilbene **23**. Upon treatment of **23** with camphorsulfonic acid to remove the methoxymethyl ether protecting groups, the fully deprotected 3-deoxyschweinfurthin B was produced in good yield.

This advanced analog was sufficiently similar to the natural product that it was submitted to our collaborators at the National Cancer Institute for bioassay. We are currently exploring methodology to introduce the other hydroxyl group into this molecule.

Key Accomplishments.

- A cascade cyclization route has been developed that leads to an advanced tricyclic olefin with the desired relative stereochemistry.
- This intermediate has been made into an aldehyde and coupled with a phosphonate representing the right half of the schweinfurthins to give a protected dideoxy derivative with the complete carbon skeleton of schweinfurthin B
- This cyclization route has been improved by introducing a Stille coupling tactic to avoid the protecting group manipulations in the original route.
- A nonracemic synthetic route has been developed based upon a cascade cyclization of an epoxide that affords an advanced tricycle intermediate with one of the requisite hydroxyl groups in place.
- This tricyclic alcohol has been converted to an aldehyde and coupled to give 3-deoxyschweinfurthin B, which is currently being tested for anti-cancer activity

Reportable Outcomes.

Abstract: Studies directed at the total synthesis of Schweinfurthin B. J. D. Neighbors, E. M. Treadwell, and D. F. Wiemer, 36th Great Lakes Regional ACS Meeting, Minneapolis, MN, June, 2002. (see appendix)

Manuscript: A Cascade Cyclization Approach the Schweinfurthin B. Treadwell, E. M.; Neighbors, J. D.; Wiemer, D. F. *Org. Lett.* **2002**, *4*, 3639-3642. (see appendix)

Abstract: Neighbors, Jeffrey D.; Wiemer, David F. A convergent approach to geranylated intermediates for synthesis of schweinfurthin B. Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003 (2003). (see appendix)

Conclusions.

Substantial progress has been made toward the synthesis of the natural product Schweinfurthin B. Two alternative cascade cyclization routes, one employing a racemic phenyl selenide and the other employing an enantioenriched epoxide, have been developed. Although we still hope to improve the yields of these cyclizations, considerable progress has been made in improving the efficiency of both routes by exploration of the Stille coupling tactics. Both routes have afforded the complete carbon skeleton of the natural product, and the epoxide cyclization has allowed the introduction of one of the hydroxyl moieties into the tricyclic left half. This key product 3-deoxyschweinfurthin B represents an important milestone, validating both our Horner-Wadsworth-Emmons coupling strategy, and our protecting group tactics. This molecule has already been sent to our collaborators at NCI for bioassay. If it shows significant bioactivity it may be of use as a probe for of the mechanism of action of this family of compounds. Even if it does not show activity, it further narrows the locus of such activity to the 3-hydroxyl group.

References.

1. Beutler, J. A.; Schoemaker, R. H.; Johnson, T.; Boyd, M. R. *J. Nat. Prod.* **1998,** *61*, 1509-1512.
2. Beutler, J. A.; Jato, J.; Cragg, G. M.; Boyd, M. R. *Nat. Prod. Lett.* **2000**, *14*, 349-404.
3. Treadwell, E. M.; Cermak, S. C.; Wiemer, D.F. *J. Org. Chem.* **1999**, *64*, 8718-8723.
4. Treadwell, E. M.; Neighbors, J. D.; Wiemer, D. F. *Org. Lett.* **2002,** *4*, 3639-3642.
5. a) Pfander, H.; Kamber, M.; battegau-Nussbaumer, Y. *Helv. Chem. Acta*, **1980**, *63*, 1367-1376. b) Meier, H.; Uebelhart, P.; Eugster, C. H. iHelv. Chem. Acta, **1986**, *69*, 106-123. c) Corey, E.J.; Noe, M. C.; Shieh, W. C. *Tetrahedron Lett.*, **1993**, *34*, 5995-5998.
6. Araki, S.; Shimizu, T.; Johar, P.S.; Jin, S-J.; Butsugan, Y. *J. Org. Chem.* **1991**, *56*, 2538-2542.
7. a) Corey, E. J.; Zhang, J. *Org. Lett.* **2001**, *3*, 3211-3214. b) Vidari, G.; Dapiaggi, A.; Zanoni, G.; Garlaschelli, L. *Tetrahedron Lett.* **1993**, *34*, 6485-6488. c) Zhang, X.; Archelas, A.; Meou, A.; Furstoss, R. *Tetrahedron Asymmetry*, **1991**, *2*, 247-250. d) see ref. 7c.

Appendices.

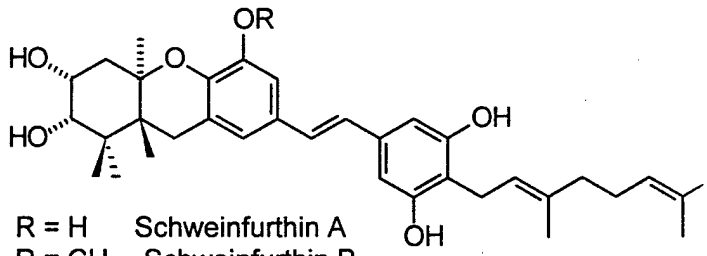
1. Abstract of: Studies directed at the total synthesis of Schweinfurthin B. J. D. Neighbors, E. M. Treadwell, and D. F. Wiemer, 36th Great Lakes Regional ACS Meeting, Minneapolis, MN, June, 2002.

2. Reprint of manuscript: A Cascade Cyclization Approach the Schweinfurthin B. Treadwell, E. M.; Neighbors, J. D.; Wiemer, D. F. *Org. Lett.* **2002**, *4*, 3639-3642.

3. Abstract of: A convergent approach to geranylated intermediates for synthesis of schweinfurthin B. Neighbors, Jeffrey D.; Wiemer, David F. 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003.

STUDIES DIRECTED AT THE TOTAL SYNTHESIS OF SCHWEINFURTHIN B. ***Jeffrey D. Neighbors***, *Edward M. Treadwell, David F. Wiemer. Department of Chemistry, University of Iowa, Iowa City, IA 52242-1294, fax: 319-335-1270*

The schweinfurthins are a small set of prenylated stilbenes recently isolated from *Macaranga schweinfurthii*, and only three of the four isolated display significant anticancer activity. These three have a common "left-half" tricycle exemplified in the structures of schweinfurthins A (**1**) and B (**2**). We envision a late stage introduction of the stilbene olefin via HWE condensation and thus require a left half tricyclic aldehyde to couple with our previously synthesized "right-half" synthon. A route involving the cationic cascade cyclization of a β-hydroxyselenide intermediate will be presented. It has been established that the phenylselenyl moiety can be used to control the diastereoselctivity of this process.



1 R = H Schweinfurthin A
2 R = CH_3 Schweinfurthin B

ORGANIC LETTERS

2002
Vol. 4, No. 21
3639−3642

A Cascade Cyclization Approach to Schweinfurthin B

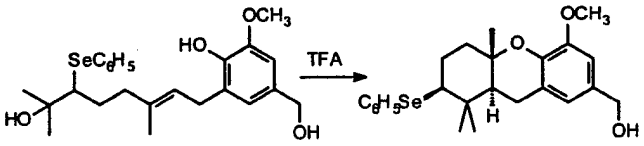
Edward M. Treadwell, Jeffrey D. Neighbors, and David F. Wiemer*

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242

david-wiemer@uiowa.edu

Received July 30, 2002

ABSTRACT



A strategy for synthesis of the hexahydroxanthene moiety of the natural products schweinfurthin A, B, and D is described. The relative stereochemistry in the key cationic cyclization step is established through the preference of the phenylselenide substituent for an equatorial orientation.

The schweinfurthins (Figure 1, **1**−**4**) are a small set of doubly prenylated stilbenes isolated from the African plant *Macaranga schweinfurthii* Pax. by Beutler et al. at the National Cancer Institute. Schweinfurthins A (**1**), B (**2**), and D (**4**) display significant activity in the NCI's 60-cell line anticancer assay with GI_{50} values less than 0.5 μM.[1,2] Their profile of activity does not match that of any clinically used anticancer agent, which suggests that these compounds may act either by a novel mechanism or at an unknown site. The schweinfurthins have been isolated in low and varying amounts from the natural source, and their absolute stereochemistry has yet to be elucidated. For these reasons, as well as their interesting biological activity, we have undertaken a total synthesis that ultimately should allow assignment of the schweinfurthins' absolute stereochemistry and provide a reliable source for further biological testing.

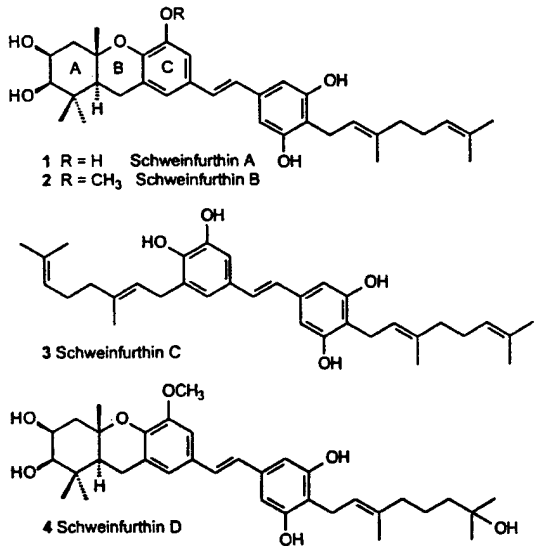


Figure 1. Structures of the schweinfurthins.

We have demonstrated the feasibility of a convergent approach to the schweinfurthins through synthesis of schweinfurthin C (**3**), the inactive congener.[3] In that synthesis, the central stilbene olefin was prepared by a Horner−Wadsworth−Emmons condensation of a benzylic phosphonate (compound **5**) and a complementary aldehyde. The phosphonate was prepared in eight steps from commercially available 3,5-dihydroxybenzoic acid (**6**) employing a directed ortho metalation for introduction of the geranyl substituent. Phosphonate **5** also could be used to advantage in preparation of the more complex schweinfurthins, provided preparation

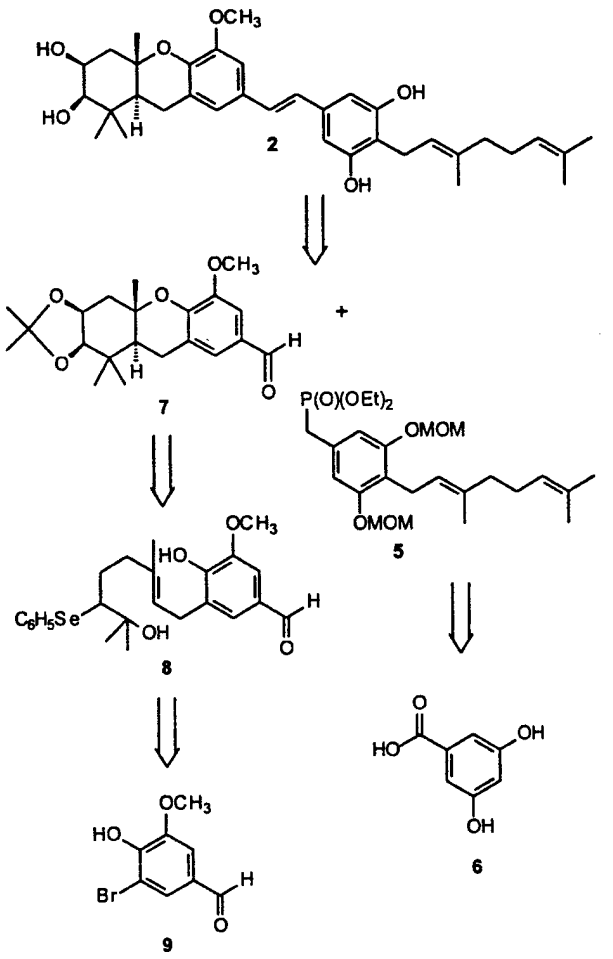
(1) Beutler, J. A.; Shoemaker, R. H.; Johnson, T.; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 1509−1512.

(2) Beutler, J. A.; Jato, J.; Cragg, G. M.; Boyd, M. R. *Nat. Prod. Lett.* **2000**, *14*, 399−404.

(3) Treadwell, E. M.; Cermak, S. C.; Wiemer, D. F. *J. Org. Chem.* **1999**, *64*, 8718−8723 and references therein.

10.1021/ol0266368 CCC: $22.00
Published on Web 09/19/2002

Scheme 1. Retrosynthetic Analysis of Schweinfurthin B



of a tricyclic aldehyde (7, Scheme 1) could be achieved. The methylated version of this tricyclic aldehyde was targeted initially because the requisite phenolic methyl ether could be carried along the sequence from the aromatic starting material, bromovanillin **9**.

One approach to the hexahydroxanthene core could be based on an acid-catalyzed cyclization to assemble both the A- and B-rings on an aromatic C-ring in a single reaction. Previous reports on cyclizations of geranylated phenols are known, but often the cyclizations occurred in low yield with numerous byproducts observed.[4,5] We hypothesized that a substituent α to the incipient carbocation could help stabilize the terminal cation, thereby possibly increasing the yield and providing an opportunity for stereocontrol. There is substantial precedent for stabilization of adjacent cations by phenylthio substituents, and some precedent for stabilization by phenylselenyl groups.[6] As shown in Figure 2, one transition state would place the phenylselenide substituent in an equatorial position with a pseudochair conformation in the incipient B-ring, while the other would require an axial phenylselenide group with a pseudoboat conformation. The use of hydroxyselenides for similar reactions has been described in two seminal papers by Kametani et al., though

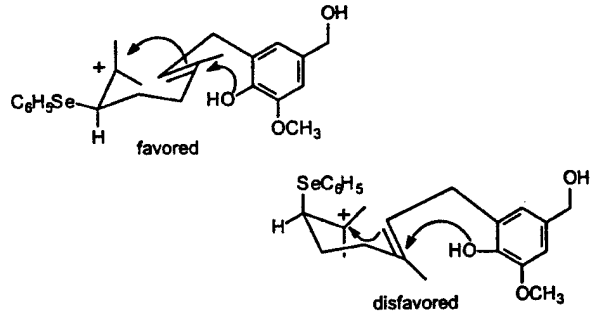
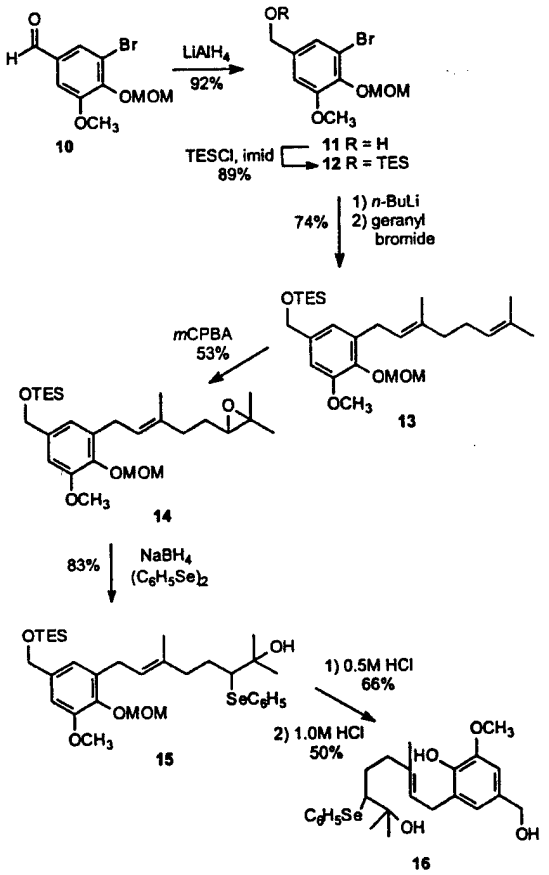


Figure 2. Possible transition states for cyclization of hydroxyselenide **8**.

application to enantiopure material was not attempted.[7] With this aim in mind, racemic β-hydroxyselenide **8** was viewed as a cyclization precursor that would allow evaluation of the viability of such an approach.

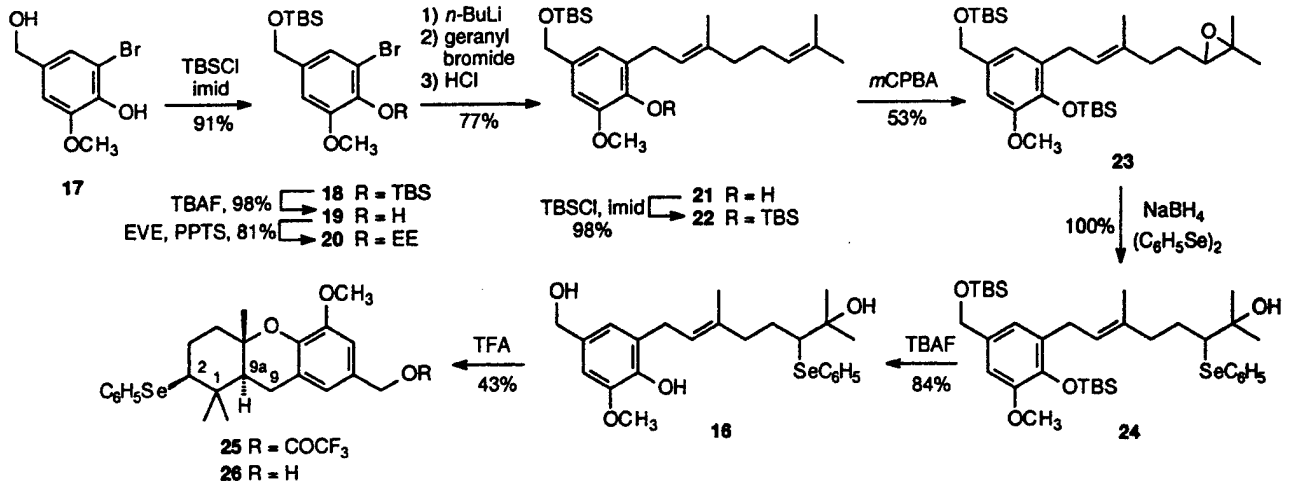
The synthesis began with preparation of the known benzaldehyde derivative **10**[8] (Scheme 2) from commercially

Scheme 2. Initial Synthesis of Hydroxyselenide **16**



available vanillin. Reduction of the aldehyde and subsequent protection of the alcohol as the triethylsilyl ether afforded

Scheme 3. Revised Synthesis of Hydroxyselenide **16**



the fully protected arene **12**, and halogen−metal exchange followed by reaction with geranyl bromide allowed installation of the geranyl chain in 74% yield. An *m*CPBA epoxidation of compound **13** initially afforded a 1:1 mixture of the regioisomeric 6,7- and 2,3-epoxides in 55% yield along with the diepoxide (7%). Even though careful column chromatography could separate the two regioisomers, the low yield of the desired product was unattractive. When the reaction was conducted at lower temperatures with slow addition of the oxidant, the yield of the desired 6,7-epoxide **14** increased to 53% along with only 8% of the 2,3-epoxide and significant recovery of the starting material (32%). Epoxide **14** reacted smoothly with phenylselenide anion generated in situ[9] to give the hydroxyselenide **15** in 83% yield.

The only transformations remaining prior to cyclization were removal of the two protecting groups, but in the best case scenario this was done through a two-step procedure. Initial treatment with 0.5 M HCl hydrolyzed the silyl ether, and subsequent treatment with 1.0 M HCl hydrolyzed the MOM acetal in an overall yield of 33%. Despite numerous attempts, all efforts at removing both protecting groups in a single step gave either incomplete deprotection or lower yields with greater byproduct formation.

A second synthetic strategy was developed to address this problematic deprotection issue. Because the silyl ether could be readily removed, it appeared attractive to protect the phenolic functionality as a silyl ether as well. However, introduction of the phenolic silyl ether would have to follow the alkylation step in the synthetic sequence, because migration of the silyl group from the oxygen to the adjacent ortho carbon has been observed in similar reactions.[10] Therefore, an ethoxyethyl-protected phenol was envisioned for the sequence up to and including the alkylation step, at which point it would be removed and a silyl ether installed in its place.[11]

Direct protection of the phenol as the ethoxyethyl ether was not successful under acidic conditions, so an indirect route was employed. The known alcohol **17**,[12] also available from vanillin, was disilylated and then selectively cleaved to the free phenol **19** by treatment with 1.0 equiv of tetrabutylammonium fluoride[13] (Scheme 3). An acid-catalyzed reaction of compound **19** with ethyl vinyl ether gave the fully protected aryl bromide **20**. This intermediate can be prepared in multigram quantities in an overall yield of 68% from vanillin without need for a chromatographic separation. Application of the halogen−metal exchange protocol and reaction with geranyl bromide afforded the analogous geranylated arene, which upon acidic workup gave the free phenol **21**. After silylation of the free phenol, the material was subjected to oxidation, and epoxide opening analogous to that used on arene **13** delivered the protected α-hydroxyselenide **24**. The deprotected target **16** could be obtained in 84% yield by treatment of the disilylated material with excess TBAF.

(4) (a) Barua, A. K.; Banerjee, S. K.; Basak, A.; Bose, P. K. *J. Indian Chem. Soc.* **1976**, *53*, 638−639. (b) Manners, G.; Jurd, L.; Stevens, K. *Tetrahedron* **1972**, *28*, 2949−2959. (c) Trammell, G. L. *Tetrahedron Lett.* **1978**, 1525−1528.

(5) Mechoulam and Yagen have reported cyclization of geranylolivetol in 88% yield, but this required heating with concentrated H_2SO_4 in nitromethane. Mechoulam, R.; Yagen, B. *Tetrahedron Lett.* **1969**, 5349−5352.

(6) (a) For a review, cf.: Harring, S. R.; Edstrom, E. D.; Livinghouse, T. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, H. W., Ed.; Jai Press: Greenwich, CT, 1992; Vol 2., pp 299−376. For more recent examples, cf.: (b) Branchaud, B. P.; Blanchette, H. S. *Tetrahedron Lett.* **2002**, *43*, 351−353. (c) Toshimitsu, A.; Hirosawa, C.; Tamao, K. *Synlett* **1996**, 465−467 and references therein.

(7) (a) Kametani, T.; Suzuki, K.; Kurobe, H.; Nemoto, H. *J. Chem. Soc., Chem. Commun.* **1979**, 1128−1129. (b) Kametani, T.; Kurobe, H.; Nemoto, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1085−87.

(8) Boger, D. L.; Jacobson, I. C. *J. Org. Chem.* **1991**, *56*, 2115−2122.

(9) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697−2699.

(10) When treated with *n*-butyllithium, both compound **18** and the TIPS analogue show a 1,3 O−C silyl migration in the only isolable products.

(11) The EE group was not carried throughout the sequence to avoid introduction of diastereomers and because the phenolic EE group was readily cleaved upon silica gel column chromatography.

(12) (a) Brink, M. *Acta Chem. Scand.* **1965**, *19*, 255−256. (b) Claus, P.; Schilling, P.; Gratzl, J. S.; Kratzl, K. *Monatsh. Chem.* **1972**, *103*, 1178−1193.

(13) Collington, E. W.; Finch, H.; Smith, I. J. *Tetrahedron Lett.* **1985**, *26*, 681−684.

To induce the desired cationic cyclization, the tertiary alcohol **16** was treated with acid under various conditions. Treatment of compound **16** with TFA afforded a single hexahydroxanthene system as the labile trifluoroacetate **25**. Purification of this product by column chromatography gave both the trifluoroacetate **25** and the parent alcohol **26** in 43% combined yield.

The relative stereochemistry of the hexahydroxanthene was assigned after extensive NMR spectroscopy on the trifluoroacetate **25**. Analysis of the coupling constants observed for the C-2 hydrogen (schweinfurthin numbering) suggested an axial disposition and hence an equatorial orientation for the phenylselenide group. The bridgehead methine hydrogen (C-9a) also appeared to be in an axial orientation on the basis of analysis of the coupling constants with the benzylic hydrogens at C-9. In this case, a COSY spectrum nicely displayed the H-9_{ax}, H-9_{eq}, H-9a spin system, indicative of a *trans*-decalin skeleton. Furthermore, the chemical shifts of the methyl groups compared favorably to those reported for a related trans-fused system but did not agree with those of a related cis-fused structure.[14] Finally, a NOESY spectrum revealed correlations (Figure 3) of the bridgehead methyl group with axial hydrogens at C-3 and C-9 and to the axial methyl group at C-1. On the other face of the molecule, complementary correlations were observed between the equatorial methyl group at C-1 and the axial hydrogen at C-9a, as well as from the axial hydrogen at C-2 to both the C-1 equatorial methyl group and the C-9 equatorial hydrogen.

The NMR data make clear that the phenylselenide substituent was successful in providing a single diastereomer of the hexahydroxanthene and may facilitate the cyclization. The equatorial disposition of the phenylselenide moiety in the final product is encouraging in that this single substituent appears to effectively govern the stereochemistry of the bridgehead centers, as expected from consideration of the transition states (Figure 2).

(14) Rouessac, A.; Rouessac, F. *Tetrahedron* **1987**, *37*, 4165−4170.

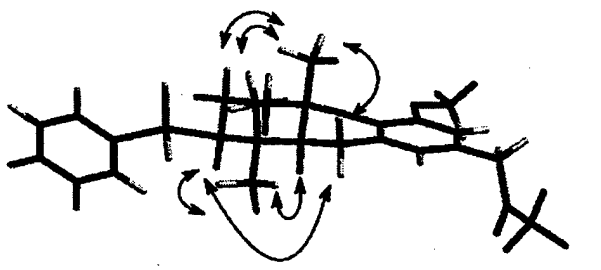


Figure 3. Selected NOESY correlations for compound **25** shown on a SPARTAN minimized structure (PM3 level).

Preparation of the tricycle **26** should allow elaboration of racemic schweinfurthin B after introduction of the A-ring hydroxyl groups and coupling with phosphonate **5**. Alternatively, now that the viability of this cyclization strategy has been shown, preparation of the epoxide **23** in nonracemic form should allow preparation of nonracemic schweinfurthin B (**2**). Our efforts to prepare the nonracemic epoxide, as well as to complete preparation of the natural products themselves, will be reported in due course.

Acknowledgment. Financial support from the DOD Breast Cancer Research Program (DAMD17-01-1-0276 and DAMD17-02-1-0423) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectral data for compounds **16**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0266368

1. **A CONVERGENT APPROACH TO GERANYLATED INTERMEDIATES FOR SYNTHESIS OF SCHWEINFURTHIN B. Jeffrey D. Neighbors** and David F. Wiemer. Department of Chemistry, University of Iowa, Iowa City, IA 52242-1294.

As part of a project aimed at synthesis of the antitumor natural product schweinfurthin B, we have explored several tactics to shorten the route to the requisite hexahydroxanthene core. The overall strategy involves cationic cyclization of an α-hydroxyselenide available from nucleophilic opening of an epoxide **1**. This epoxide is available via multiple routes, some of which would be amenable to preparation of nonracemic material if the aryl bromide **2** could be coupled to a geranyl chain bearing an epoxide (e.g. **3**). Our investigations of various methods for coupling these components will be presented.